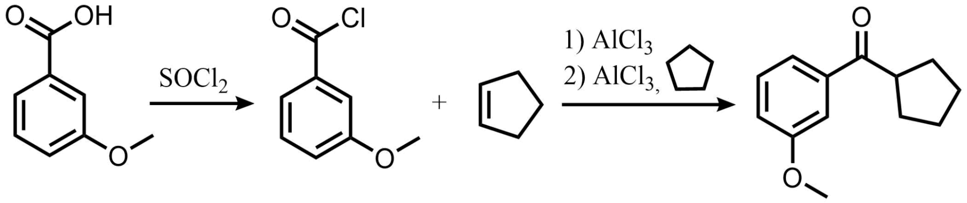
by arclightshroom

SYNTHESIS OF KETAMINE ANALOGUE MXE AND PURIFICATION OF RAW MATERIALS VIA DCVC

Despite MXE being (from a synthetical point of view) identical to ketamine I thought it deserved a paper on its own considering how popular it was in the RC scene before disappearing. To make this a worthwhile read and a good resource to amateur chemistry I decided after a failed distillation attempt to include a detailed guide on dry vacuum column chromatography, a technique used to quickly and easily purify bulk quantities of compounds with minimal silica and solvent use. The thermal rearrangement procedure was also optimized.

Synthesis of 3-methoxyphenyl cyclopentyl ketone

Ketamine and its analogues are usually made from the corresponding phenyl cyclopentyl ketone, which is usually made with a Grignard reaction between the benzonitrile and cyclopentyl bromide or a Friedel-Crafts between the benzoyl chloride and cyclopentene. The Grignard reaction (which I still consider superior for the synthesis of ketamine) will not be attempted due to cost concerns. 3-meo-benzonitrile is too expensive for a starting material, and its synthesis too inconvenient, 3-meo-benzoyl chloride on the other hand is easily and quantitatively made from the cheap and commercially available m-anisic acid.



Synthesis of 3-methoxybenzoyl chloride (m-anisoyl chloride):

To 400g m-anisic acid 1L of thionyl chloride is added, and the mixture refluxed until gas evolution ceased. The reflux condenser is swapped for a distillation head, and all the excess thionyl chloride is distilled off at normal pressure. Once it stops distilling, vacuum is slowly turned on and a single fraction coming over at 106.5°C is collected at 6mmHg. 435g of 3-methoxybenzoyl chloride are collected in almost quantitative yield.
NOTE: Shouldn't even say it but, thionyl chloride reacts releasing hydrogen chloride and sulfur dioxide. Before attempting this large scale reaction I ran multiple tests to get everything in check. I also own a fume hood.

Friedel-crafts reaction:

18.3g of 3-methoxybenzoyl chloride to 60mL of DCM followed by 16.5g anhydrous aluminum chloride (1.15eq.) under an atmosphere of nitrogen. 8.1g of cyclopentene (1.1eq.) were added dropwise at a temperature of -10 to -5°C, after the addition the mixture is then stirred 1 hour cold. Another 16.5g aluminum chloride and 30mL cyclopentane are added and the mixture refluxed for 3h. After cooling, the reaction solution is added dropwise to a stirring mixture of 200mL DCM and 600mL at such drop rate to keep everything at room temperature, external cooling might be useful for faster addition rate. The DCM layer is then separated, dried with sodium sulfate and removed under vacuum to yield a thick dark red oil.

Vacuum distillation was set up to purificate the oil, but at 6mmHg, which is the max pressure my pump can reach, the distillate was coming over at around 180°C, which caused significant decomposition. Only 5g grams of dark yellow oil were collected, the rest turned into tar in the distilling flask. This essentially leaves 3 possibilities, continuing with a dirty starting material, buying a better pump or column chromatography. The dark red oil turns black on standing (contrary to the clean purified ketone) and from my personal experience starting a synthesis with a tar black reagent only adds problems, so I was determined to clean it. I don't currently have the finance for a serious vacuum pump, and the thought of doing a standard flash column for anything over a few grams of product was disturbing. Fortunately I was recommended DCVC by other friends, which is a chromatographic technique ideal for quick purification of bulk quantity materials with minimal solvent waste. It can be thought of a preparative TLC.

Purification of crude 3-methoxyphenyl cyclopentyl ketone via DCVC:

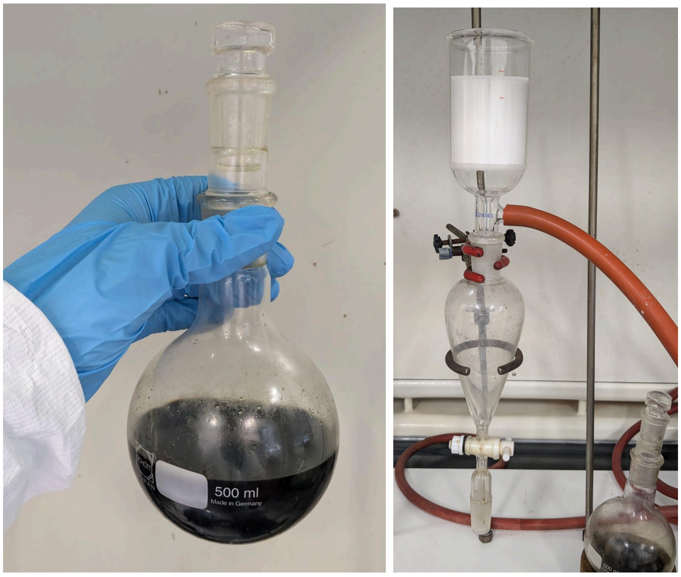
To show the capabilities of this technique, and to do everything once and be done with it, I repeated the above Friedel-Crafts procedure on a 366g scale, obtaining around 300g of crude product.

Stationary phase: Silica Gel 60 - 0.015-0.040mm. Fine (15-40μm) silica is important, standard gel (40-60μm) or coarser won't work at all. The smallest particle size the better, 15-40μm is the best.

Eluent: All solvents used in flash chromatography can be used. Low boiling solvents (ether, DCM, pentane, ..) can cause problems with the vacuum and should be avoided. I ran this column with a hexane:EtOAc gradient, contrary to standard flash DCVC doesn't crack under abrupt polarity change, so I went with 5-10% EtOAc increments.

Equipment:

- Sintered glass funnel, at least 10cm height, width depends on the scale you are running the column. Separation efficiency depends on silica surface area and not height, for a 300g separation I used a 7cm wide funnel. As a note, 7cm for 300g is a lot small, ideally it would be double that, but considering this was an easy separation (my ketone and the tar have vastly different polarities) it worked. For closer polarity gaps aim at 0.5-1cm for every 10g or 2.5-3cm per 10g for difficult separations.
- Sep funnel to connect the "column"
- Vacuum pump, membrane or water aspirator, absolutely not an oil pump. A soft vacuum like the one used for filtrations is perfect.



Crude 3-methoxyphenyl cyclopentyl ketone + setup used for DCVC

Packing the column: the column has to be packet dry as this method requires the silica to be extremely compact. Without proper packing this method will not work at all.

- First, silica is added to the funnel, we want a packed column height of 5cm, so loose silica should be around 7-8cm. 15-40µm silica is extremely powdery, it flies everywhere and it's very toxic by inhalation. Pour the silica CAREFULLY and inside a hood (if not available be sure to protect yourself with appropriate mask and PPE, do not breathe the dust in).
- Tap the column to evenly distribute the silica, then turn on the vacuum and pack the column by pressing the surface with a hard object. I used a mortar pestle. Use quite a bit of force, it has to be very compressed.
- Level the surface, especially the sides. You can do this by turning the vacuum off, scraping the surface a bit, turning the vacuum back on and press the surface again trying to make it as smooth as possible. Use a spatula to level the edges near the glass.
- Add a filter paper on top to protect the surface

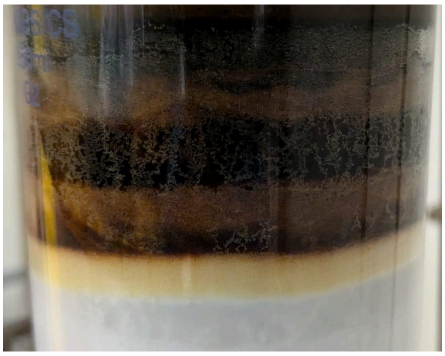
Preparing the column: Vacuum was turned off, hexane was added and vacuum turned on again, add hexane until the column is completely wet with solvent and some is dripping in the sep funnel. Pay attention to the solvent front, it should descend with a straight homogeneous line. If the solvent front is not straight, the column is not packed correctly.

Loading the column: Dry loading is the fool proof way, but I decided to use wet loading as I thought it was better for an oily substance like this and my column was too short to load that much celite.

- Dry loading: dissolve your compound in a suitable solvent, add celite (eyeball it, enough to hold on your compound) and rotovap everything dry. Then add the dry celite/product mix on top of the column, and press it. This doesn't need to be packed as tight. Add a filter paper on top of the celite layer.
- Wet loading: simply add the liquid on top of the column having care to distribute it evenly. There has to be a layer of solvent present so that the product does not go into the silica immediately. Do this with vacuum off, the oil shoul "fall" in the hexane and pool above the filter paper. If it's a solid compound dry load or dissolve in minimal solvent.

Running the column: Vacuum is turned on and the solent/compound allowed to penetrate the silica. Solvent will drip in the sep funnel, and when you are ready to collect a fraction simply shut off the vacuum, repressurize, open the funnel and collect. Continuously add solvent on top. When to change the eluent composition and when to collect a fraction is basically eyeballing, especially if the compounds you are trying to separate are not colored like mine.

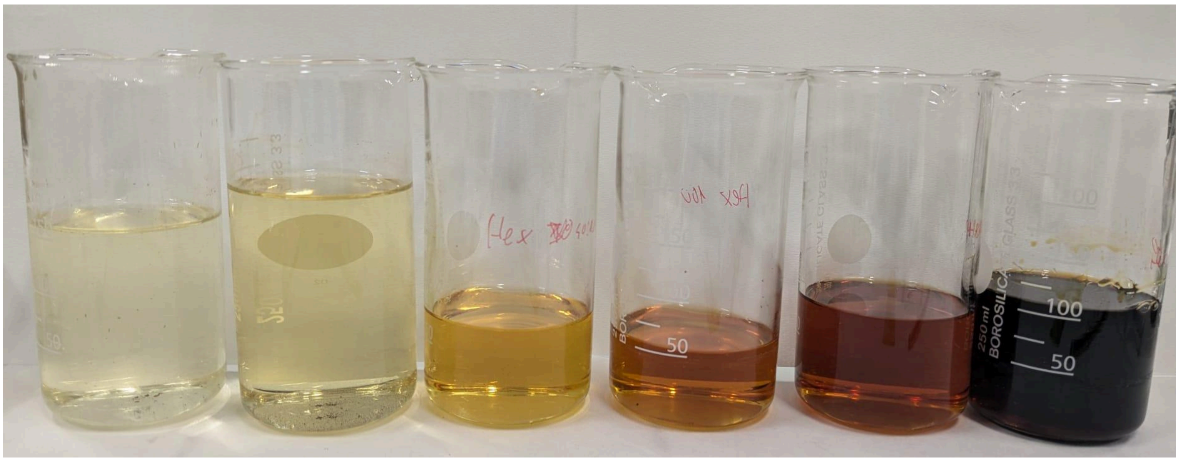
- If running isocratic elution, just keep adding solvent and collect fraction until satisfied.
- If running gradient, increase the polarity of the eluent until the desired compound elutes. Slow down at the optimum to increase separation efficiency.



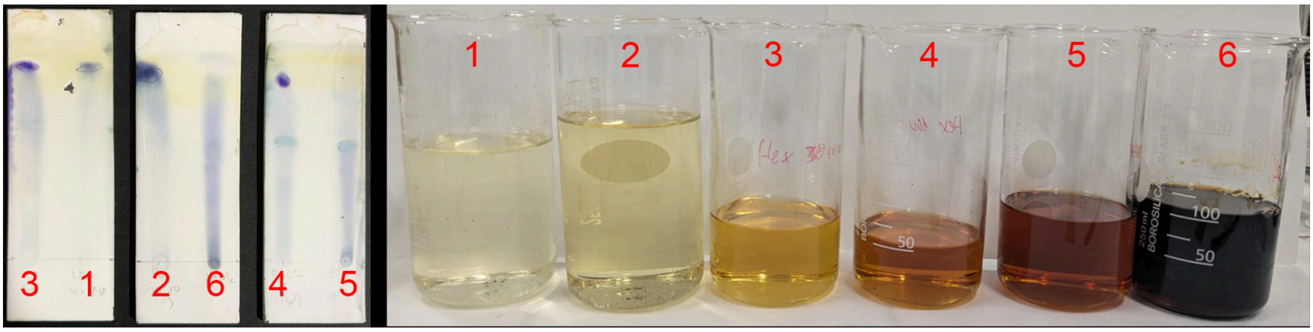
In this case it's pretty easy to see the separation happening

For 3-methoxyphenyl cyclopentyl ketone, the column was runned as following:

- Column prepared with 100% hexane
- First fraction: 100% hexane
- Second fraction: 100% hexane to 10% EtOAc in hexane, 2x5% increments
- Third fraction: 10% to 15% EtOAc, single 5% increment
- Fourth fraction: 15% to 25% EtOAc, single 10% increment
- Fifth fraction: 25% to 50% EtOAc, single 25% increment
- Sixth fraction: 50% to 100% EtOAc, 2x25% increments



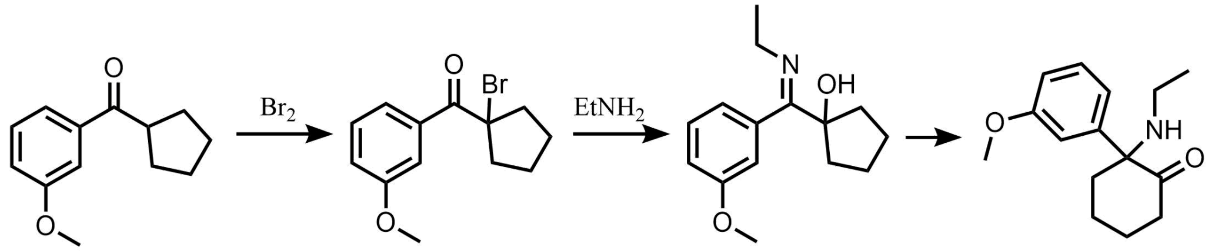
All the fractions were analyzed with TLC to determine what to keep. Eluent: 15% EtOAc in hexane, visualized with vanillin stain.



The compound of my interest should be the one with Rf 0.81. I decided to keep the fractions from 1 to 4. Fractions 1,2 and 3 were pooled together, while 4 was kept separate since it looked like it contained some product, but it was also tarry and contained a second compound with Rf 0.55. The pooled fractions were reduced on the rotovap to afford 220g of 3-methoxyphenyl cyclopentyl ketone in 50.2% yield.

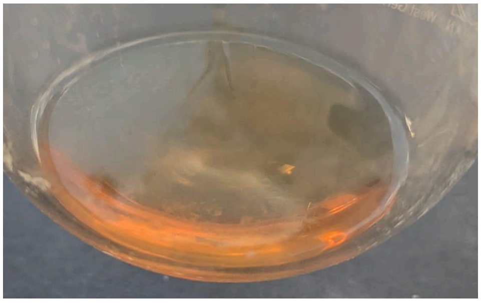
Overall, it was not my first time doing column chromatography, but it was my first DCVC, so many things can be improved. This whole process took less than an hour and about 1 liter of solvent for 200g of material, which I must say it's amazing. The streaking on the plates made me worry a little, but after testing the ketone in the HPLC I obtained a single clean peak with 100% area, so it looks like the separation worked better than expected. HPLC-DAD chromatogram and chromatographic conditions reported in the analytical section.

MXE via thermal rearrangement



Bromination:
5g of 3-methoxyphenyl cyclopentyl ketone are dissolved in 40mL dry DCM and 1mL GAA is added. A solution of 4.37g of bromine (1.1eq) in 10mL DCM is prepared, 2-3mL are added directly to the reaction mixture and left stirring until the reaction heats up and HBr fumes are visible. At this point a cold water bath is added and the rest of the bromine solution added dropwise. Everything is then stirred at room temperature for an hour, the reaction mixture is then washed with 2x20mL sodium bisulfite solution and 2x20mL sodium carbonate solution. The organic phase is dried with sodium sulfate and filtered through a silica plug to remove impurities. The solvent is removed under vacuum to give 4.9g of bromoketone in 71% yield.
NOTE: An alternative bromination method would be to dissolve the bromoketone in 1.5 equivalents of 48% HBr and add 30% hydrogen peroxide dropwise. Care as excess peroxide could degrade the product. The bromoketone is very unstable and must be used immediately.

Bromoketone without silica plug purification


Bromoketone with silica plug purification

Imine formation:
4.9g of bromoketone are dissolved in 5mL methanol and cooled in an ice bath, then 3.58g of dry potassium carbonate are added. Once cold, 3.14g of anhydrous ethylamine (4eq) is added portionwise to keep temperature at around 0°C. The solution is left 2 days in the freezer, then stirred at room temperature for 5h, filtered and distilled dry under vacuum, leaving a dark brown goop. The crude freebase is redissolved in ether in a flask and its HCl salt precipitated with dry hydrogen chloride gas. The ether is decanted off and the powder rinsed with fresh ether until no color is present. The powder is then dried by pulling a vacuum on the flask with gentle heat. 1.96g of hydrochloride salt was recovered with a 40% yield.
NOTE: The hydroxy imine is supposedly water stable, but when treated with aqueous HCl black tar was obtained instead of a white solid. Keeping the reaction cold definitely improves the process, as two previous tests of 2h and 2 days reaction time at room temperature gave sub 10% yield of a brown tarry substance that was impossible to clean. I even tried rearranging it directly, but from 1g bromoketone I've obtained a sad 20mg of MXE after the rearrangement. Running it 2 days at -20°C not only improved the yield drastically but also gave something that was not tar. I'm not sure what side reaction happens at room temperature as this imine is troublesome to analyze as it's unstable in silica, hydrolyzes so no useful TLC and the HPLC I have access to doesn't have mass spec, so I'd need standards, which I don't

have. One theory could be direct substitution of the bromine with ethylamine, or just polymerization crap. I’m not sure of the shelf life of this compound, I didn’t want to risk it so I used it immediately after. Also, the hydroxy imine HCl is deliquescent and it melts if it stays too long in open air exposed to moisture, instead of filtering I opted for solvent wash and decantation. A centrifuge might come handy for this compound.

Hydroxyimine HCl precipitate from ether

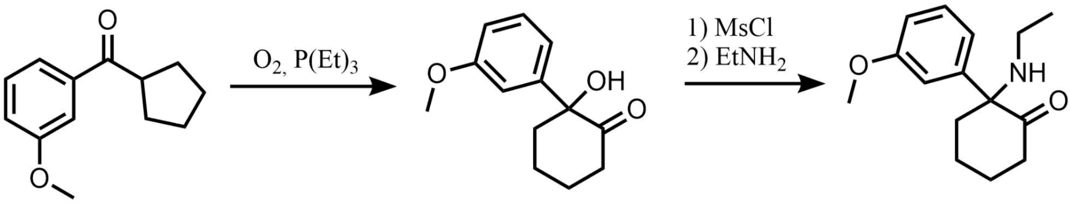
Thermal rearrangement:

1.96g of 3-methoxy hydroxylimine HCl are suspended with stirring in 20mL of 1,2-dichlorobenzene and refluxed for 40 minutes under nitrogen. After cooling the organic layer is extracted with 1M HCl and basified after washing with DCM. The basic solution is extracted with DCM and reduced under vacuum. The resulting brown oil is dissolved in IPA and concentrated HCl is added, crystals are filtered off, then the IPA solution is distilled dry, more crystals appear, and are washed with acetone. In total 880mg of clean white crystals are obtained with a 45% yield.

NOTE: In another experiment I’ve tried to rearrange the imine in ethyl benzoate with aluminum chloride at 125°C for 5 hour, the imine didn’t survive the treatment, and nothing but tar was obtained.

MXE HCl precipitating from IPA

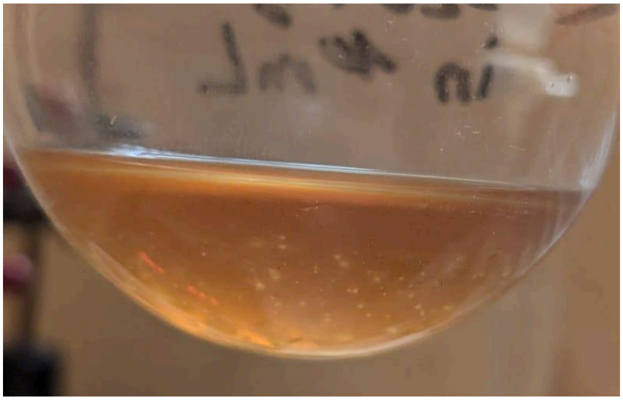
MXE via mesyl chloride



Autoxidation ring expansion:

20g of 3-methoxyphenyl cyclopentyl ketone, 24.4g of triethyl phosphite (1.5eq.) and 5.5g of KOH (1eq.) where all added to 200mL ethanol, the flask is then purged with oxygen and

stirred at 30°C for 48h with an oxygen balloon. Most ethanol was removed under vacuum, and the slurry added to 600mL cold water and stirred strongly for 1h in an ice bath. Excess water is separated by decantation, the solid washed with more water, vacuum filtered then dried in a vacuum desiccator to yield 15.53g of yellowish solid in 72% yield.
NOTE: This compound behaves weirdly. I've run 7 tests at 0.5 to 20g scale and the compound unpredictably appears as a yellowish solid, a yellow semisolid (looking like wet mud even if dry) or a thick yellow liquid. HPLC confirmed (see analytical section) that it's the same chemical, but I didn't manage to crystallize it in any way. Slow evaporation from acetone afforded crystals shards, but they melted again after a while, analysis indicates that's likely caused by impurity. Column or probably just a silica plug would take care of this, but since the alcohol purity was consistently >90% I just went on with the amination step.



Liquid alcohol

Solid alcohol after water washings

Mesyl chloride amination:
10g of 2-(3-methoxyphenyl)-2-hydroxycyclohexanone were dissolved in 6mL THF, 16g of triethylamine (3.5eq) were added and the mixture cooled in a salted ice bath. The flask was then purged with nitrogen, and a solution of 15.5g mesyl chloride (3eq) in 20mL THF was added dropwise keeping the temperature at 0°C. After finishing the dropping, the mixture was stirred for another 1h, 14.3g anhydrous ethylamine (7eq) was then added and left stirring another 4 hours at room temperature. Most of the THF was removed under vacuum, 50mL of water and 50mL of DCM were then added, the organic layer separated and extracted 1M HCl. After basification with NaOH, MXE freebase was extracted with DCM and reduced under vacuum. The resulting oil is dissolved in IPA and the HCl salt precipitated with dry hydrogen chloride gas, the solid was suspended in refluxing acetone and water was added drop by drop until dissolution. Crystals form on cooling, giving 5.27g of MXE HCl in 41% yield.

MXE HCl after crystallization

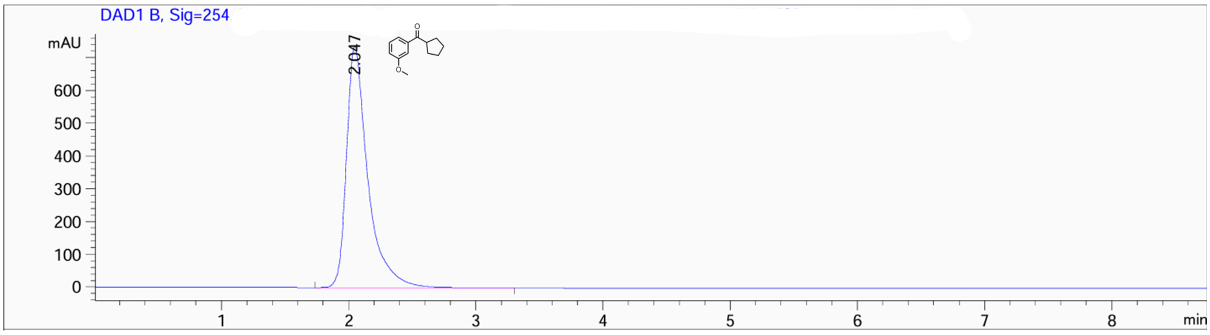
Analytical section

HPLC-DAD chromatogram:

Chromatographic conditions: 1mL/min, room temp., isocratic ACN, C18 column, 10µL injection volume. Samples prepared at 1mg/mL.

3-methoxyphenyl cyclopentyl ketone:

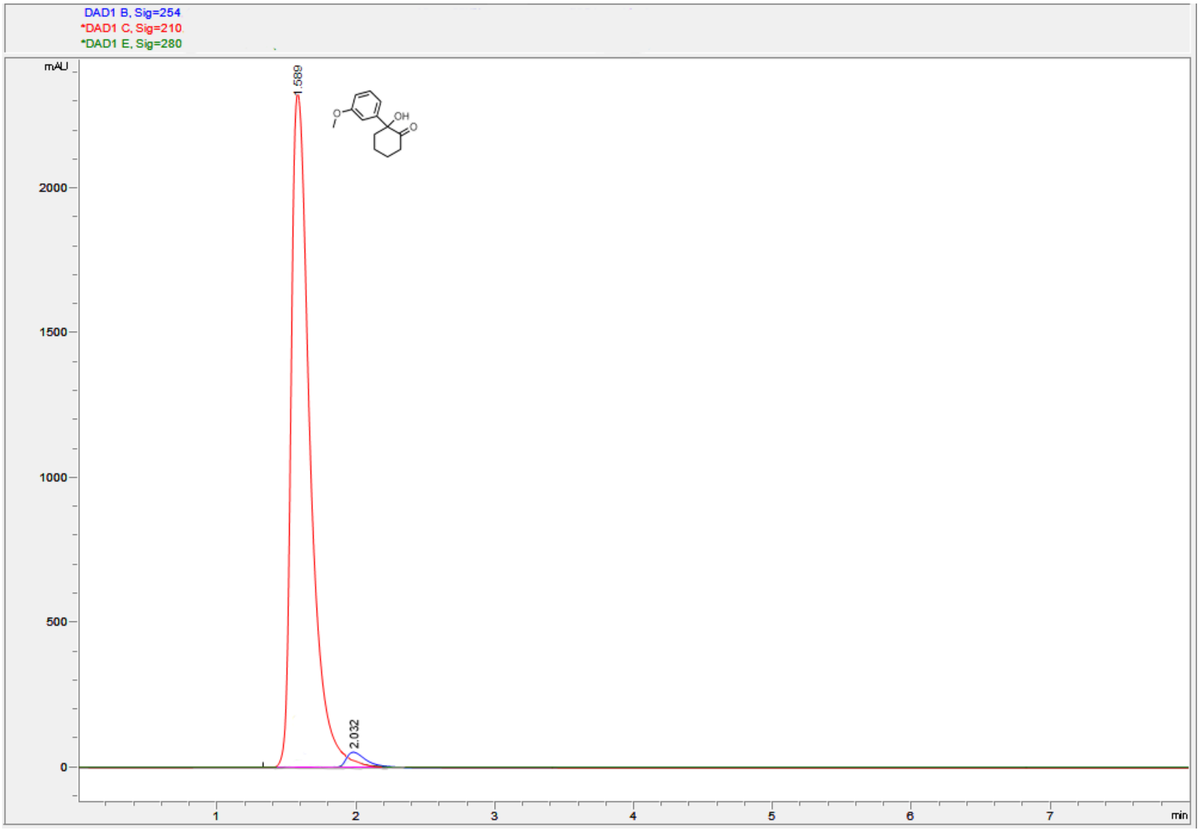
Analyzed after DCVC purification, various UV wavelengths were tested, peak absorbance was found at 254nm.



Retention time: 2.047min
Area: 100%

2-(3-methoxyphenyl)-2-hydroxycyclohexanone:

Both solid and honey-like samples were analyzed, both gave peaks at 210nm at 1.4 to 1.5 retention times, with an impurity coming out at around 2 (peak absorbance at 254nm), which presumably is unreacted ketone.



Retention time: 1.4 to 1.5 minutes
Area: 97.73%

As both samples elute equally it’s reasonable to assume that they are the same substance. Out of the sample I’ve tested purity ranges from 93-98% (best run shown), where the 98% was solid. Another key difference was smell, while the crystalline material is practically odorless the other still reek of triethyl phosphite. Without mass I cannot see and identify contaminants without a standard, and I forgot to inject triethyl phosphite, so I don’t know precisely how much there is, but based on smell quite a bit. My best guess is that 5-7% unreacted ketone is enough to prevent crystallization, and it likely holds on triethyl phosphite too. It’s also possible that other impurities not visible at the wavelengths I tested are present.

TLC data:
Visualized with vanillin stain

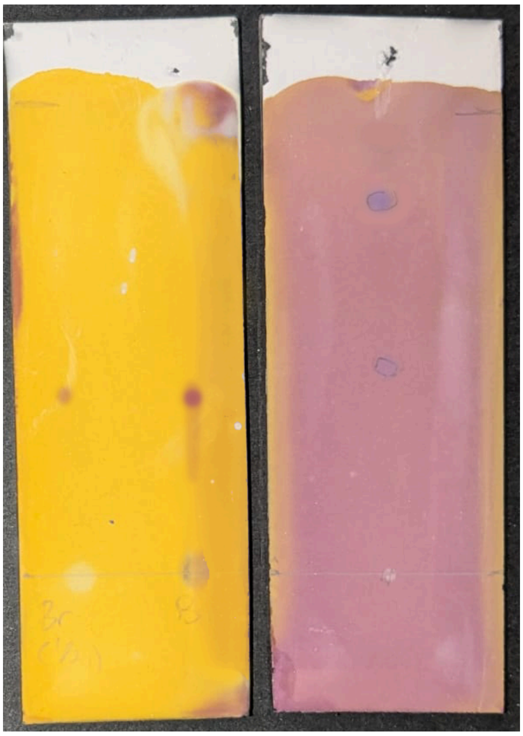
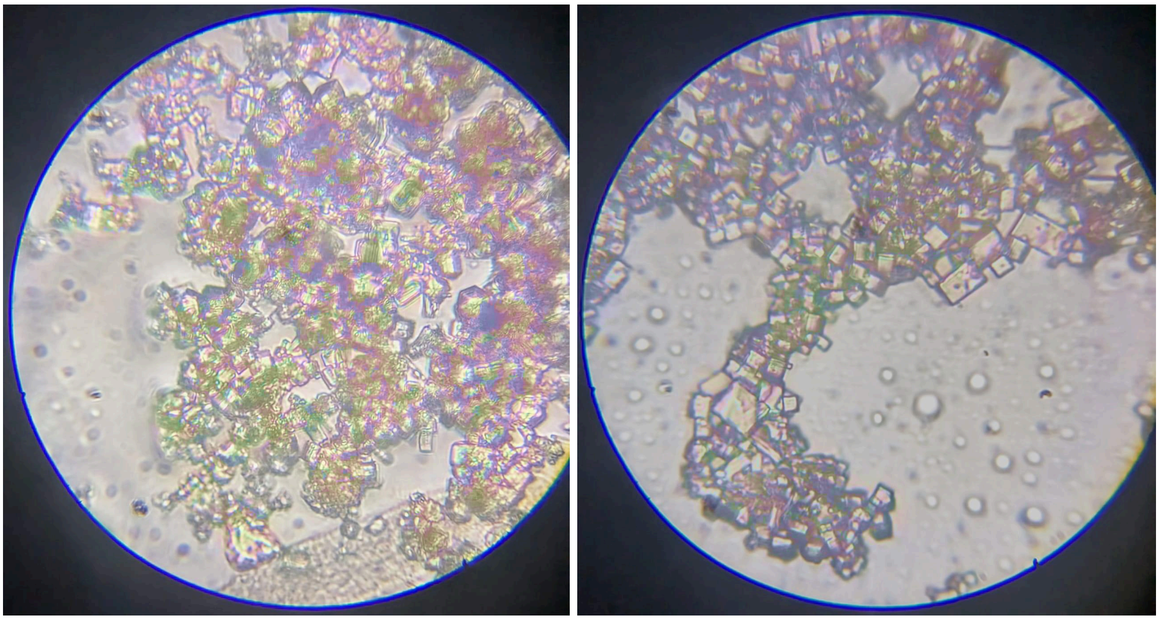


Plate 1: Bromoketone, eluent: 1:10 EtOAc:hexane. First sample is after purification, second is before. Rf: 0.38
Plate 2: MXE freebase, from mesyl chloride reaction. Eluent: 1:10 EtOAc:hexane with a drop of concentrated ammonia. Rf: 0.78. Another spot present at Rf: 0.44
Wasn’t able to get a decent plate of the imine, the impure goop was a mess of tar, and I suspect that it’s unstable on silica. I unfortunately forgot to analyze the alcohol from the oxidative ring expansion.

Crystalline structure:
Contrary to ketamine, which makes needles, this substance crystallizes in flat slabs made of square crystals. Under the microscope these structures make some cool iridescent hue! I know it’s an artifact, but it’s still very pretty.



Thanks for reading, all of this is just for the science and helping the community. Here’s a Monero address if you like my work and wish to support, every donation helps, if you feel like it!
43FQm5egGq3Wa3wwxetWdXNMDjwpfmzPjXcjCR8EDvtKYF93hT7KcXg2upVURcwnTPMFpg5GYGfg2LYpX5p6ybGc3qQN8cd

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